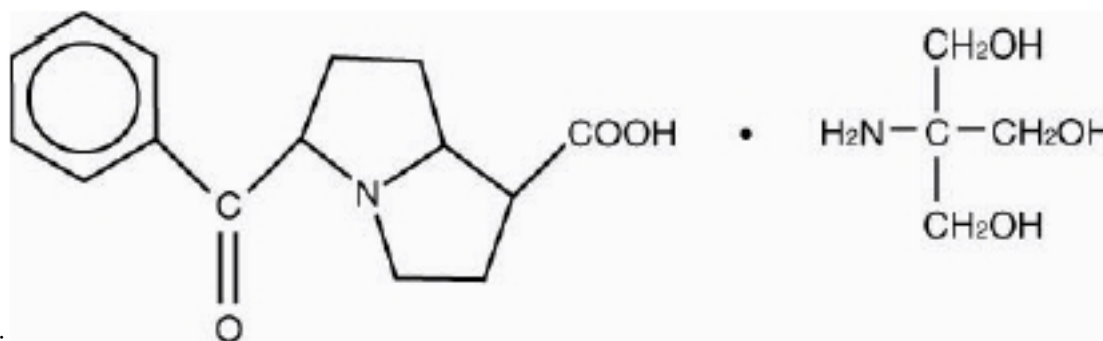


## ACULAR PF - ketorolac tromethamine solution

Allergan

### DESCRIPTION

ACULAR<sup>®</sup> PF (ketorolac tromethamine ophthalmic solution) Preservative-Free is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) and it has the following



structure:

ACULAR<sup>®</sup> PF is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of ACULAR<sup>®</sup> PF is 290 mOsm/kg.

Each ml of ACULAR<sup>®</sup> PF contains: **Active:** ketorolac tromethamine 0.5%. **Inactives:** purified water; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4.

### CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

One drop (0.05 mL) of ketorolac tromethamine (preserved) was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

In two double-masked, multi-centered, parallel-group studies, 340 patients who had undergone incisional refractive surgery received ACULAR<sup>®</sup> PF or its vehicle QID for up to 3 days. Significant differences favored ACULAR<sup>®</sup> PF for the treatment of ocular pain and photophobia.

Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure.

### INDICATIONS AND USAGE

ACULAR<sup>®</sup> PF ophthalmic solution is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery.

### CONTRAINDICATIONS

ACULAR<sup>®</sup> PF ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

### WARNINGS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

## PRECAUTIONS

### **General:**

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening.

Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that ACULAR® PF ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

### **Information for Patients:**

ACULAR® PF should not be administered while wearing contact lenses.

The solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration. To avoid contamination, do not touch tip of unit-dose vial to eye or any other surface.

### **Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

### **Pregnancy:**

**Teratogenic Effects: Pregnancy Category C.** Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. ACULAR® PF ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects:** Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACULAR® PF ophthalmic solution during late pregnancy should be avoided.

### **Nursing Mothers:**

Caution should be exercised when ACULAR® PF is administered to a nursing woman.

### **Pediatric Use:**

Safety and efficacy in pediatric patients below the age of 3 years have not been established.

### **Geriatric Use:**

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

## ADVERSE REACTIONS

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by approximately 20% of patients participating in clinical trials.

Other adverse events occurring approximately 1 - 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis, and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions include: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

**Clinical Practice:** The following events have been identified during postmarketing use of ketorolac tromethamine ophthalmic solution 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solution 0.5%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see **PRECAUTIONS, General**).

## **DOSAGE AND ADMINISTRATION**

The recommended dose of ACULAR<sup>®</sup> PF is one drop (0.25 mg) four times a day in the operated eye as needed for pain and photophobia for up to 3 days after incisional refractive surgery.

## **HOW SUPPLIED**

ACULAR<sup>®</sup> PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is available as a sterile solution supplied in clear, LDPE, single-use vials as follows:

ACULAR<sup>®</sup> PF 12 Single-Use Vials 0.4 mL each: **NDC 0023-9055-04**

Store ACULAR<sup>®</sup> PF at 15°C-30°C (59°F - 86°F) with protection from light.

**Rx only**

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